

Complete Summary

GUIDELINE TITLE

Single-agent interleukin-2 in the treatment of metastatic melanoma: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Petrella T, Quirt I, Verma S, Haynes A, Charette M, Bak K, Melanoma Disease Site Group. Single-agent interleukin-2 in the treatment of metastatic melanoma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Mar 20. 32 p. (Evidence-based series; no. 8-5). [32 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

Metastatic melanoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Dermatology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate the role of single-agent interleukin-2 (IL-2) in the treatment of adults with metastatic melanoma
- To determine the appropriate patient population to be considered for treatment, if there is a role for single-agent IL-2
- To determine the appropriate dose and schedule, if there is a role for single-agent IL-2
- To evaluate the toxicities associated with IL-2

TARGET POPULATION

Adults with metastatic melanoma

INTERVENTIONS AND PRACTICES CONSIDERED

Single-agent interleukin-2 (IL-2)

MAJOR OUTCOMES CONSIDERED

Primary outcomes of interest

- Objective response rates
- Complete response rates
- Duration of response
- Toxicity
- Quality of life

Secondary outcomes of interest

- Progression-free survival
- Overall survival

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Searches were performed in the following databases: MEDLINE (1985 through March week 5, 2006), EMBASE (1985 through 2006 week 14), and the Cochrane Library (2006, Issue 1). "Melanoma" (Medical Subject Heading [MeSH] and text word) was combined with "interleukin-2" (MeSH and text word) or "IL-2" (text word). Those terms were then combined with search terms to locate practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and phase II trials.

In addition, the proceedings of the annual meeting of the American Society of Clinical Oncology (1997-2005) were searched for reports of newly completed or ongoing trials. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

The following types of articles were selected for inclusion in this systematic review of the evidence:

1. Full reports or abstracts of randomized controlled trials or randomized phase II trials in which one trial arm involved single-agent interleukin-2 for patients with metastatic melanoma
2. Full reports or abstracts of single-arm phase II trials of single-agent interleukin-2 for patients with metastatic melanoma, which were included because insufficient evidence was available from randomized controlled trials
3. Meta-analyses of randomized controlled trials, systematic reviews, and evidence-based practice guidelines

Exclusion Criteria

1. Papers published in a language other than English were not considered due to limited resources for translation.
2. Phase I studies were not considered.
3. Reports that provided data for a sample of less than 10 patients with metastatic melanoma were excluded.

NUMBER OF SOURCE DOCUMENTS

One systematic review, five randomized trials comparing single-agent interleukin-2 (IL-2) versus IL-2 combination therapy, and 12 single arm phase II trials were eligible for inclusion in this systematic review of the evidence. In addition, one quality of life (QOL) report for patients included in one of the randomized trials was identified.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

None of the randomized controlled trials compared single-agent interleukin-2 (IL-2) to standard therapy or to placebo. In addition, the randomized controlled trials included different regimens and doses of IL-2 as well as combining IL-2 with different agents (lymphokine-activated killer cells, interferon, and histamine dihydrochloride). Due to the heterogeneity between the randomized controlled trials, the Melanoma Disease Site Group (DSG) decided against conducting a meta-analysis of the results.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by two members of the PEBC Melanoma Disease Site Group (DSG) and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on IL-2 in metastatic melanoma. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of the clinical practice guideline developed by the Melanoma DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada.

Disease Site Group Consensus Process

The guideline was circulated for review and discussion by the Melanoma DSG on June 21, 2005. Most of the members conceded that given the available data, it would be optimal to use IL-2 as first line therapy in a select group of patients when disease burden is at its lowest. However, it should be noted that one member of the Melanoma DSG was not comfortable with the recommendations set out in this document, stating that IL-2 "is and remains an investigational drug" and thus should not be used as standard therapy.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External Review

Following review and discussion of sections 1 and 2 of this evidence-based series, the Melanoma Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Feedback was obtained through a mailed survey of 276 practitioners in Ontario (medical oncologists, radiation oncologists and surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the recommendations and whether the recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on July 8, 2005. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Melanoma DSG reviewed the results of the survey.

Report Approval Panel

The final Evidence-based Series report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel in May, 2006. The Panel consists of two members including an oncologist, with expertise in clinical and methodology issues.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

There are no studies that compare interleukin-2 (IL-2) to the current standard of care, dacarbazine (DTIC), or to placebo in the treatment of metastatic melanoma.

- After weighing and reviewing the evidence that does exist, the opinion of the Melanoma Disease Site Group is that high-dose IL-2 is a reasonable treatment option for a select group of patients with metastatic melanoma:

- Patients should have a good performance status (Eastern Cooperative Oncology Group [ECOG] 0-1), and a normal lactate dehydrogenase (LDH) level.
- Patients should have less than three organs involved or have cutaneous and/or subcutaneous metastases only and no evidence of central nervous system metastases. In this select group of patients IL-2 treatment can produce durable complete remissions.
- The recommended dose and schedule of high-dose IL-2 is 600,000 IU/kg/dose intravenously over 15 minutes, every eight hours, for a maximum of 14 doses.
- If high-dose IL-2 is delivered, the recommendation is that it be done in a tertiary care facility with staff trained in the provision of this treatment with appropriate monitoring.
- To facilitate patient treatment and develop expertise in this therapeutic modality, the recommendation is that high-dose IL-2 programs be established in one or two centres in Ontario.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by one systematic review, randomized trials, single arm phase II trials, and one quality of life (QOL) report.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Data from three randomized controlled trials has demonstrated that single-agent interleukin-2 (IL-2), when given in high doses, can elicit an objective response rate of 5% to 27% with complete responses in 0% to 4% of patients.
 - Similarly several non-comparative phase II trials of high-dose single-agent IL-2 have consistently reported objective response rates of 10% to 33% with complete responses ranging from 0% to 15%.
- High-dose IL-2, as a single agent or in combination with lymphokine-activated killer (LAK) cells, can elicit long-term responses in select patients.
 - The three randomized trials demonstrate that in the 0% to 11% of patients, who are complete responders, there have been consistent observations of long-term responses that range from 6 to 66+ months (median 27 months).
 - Complete responders in phase II trials have also demonstrated impressive long-term responses that range from 1.5 to 148 months (median 70 months).
 - No other therapy for metastatic melanoma offers the possibility for a durable complete remission.

See the original guideline document for a detailed review of the factors associated with response to IL-2 and the recommended dose and schedule of high-dose IL-2.

POTENTIAL HARMS

High-dose interleukin-2 therapy has considerable grade 3/4 toxicity. Three randomized controlled trials of high-dose IL-2 and eight noncomparative phase II trials of single-agent high-dose interleukin-2 have reported the following types of grade 3/4 adverse effects: gastrointestinal (range 0-76%), cardiovascular (range 0-74%), renal (range 0-87%), neurologic (range 0-29%), hematologic (range 0-71%), febrile neutropenia (range 4-88%), sepsis (range 0-63%) and hepatic (0-90%). Those toxicities are manageable with the use of available guidelines and trained staff.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- High dose interleukin-2 (IL-2) has similar response rates to our standard chemotherapy; however, the low but durable complete response seen with IL-2 is very rare with chemotherapy and may lead to years of benefit for patients.
- Based on the available data assessing prognostic factors and patient selection, patients with non-visceral metastases and fewer metastatic sites have a much higher response rate. In these select patients, high dose interleukin-2 may be considered first line therapy.
- Recommendations for this guideline are based largely on phase II data and very little phase III data due to the lack of availability of large randomized trials comparing IL-2 to dacarbazine (DTIC) or other chemotherapy. Further randomized data will not be available as there are currently no ongoing or planned randomized trials. IL-2 is currently widely used in the United States and is an approved therapy in both Canada and the United States.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Mar 20

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Melanoma Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Melanoma DSG disclosed information on potential conflicts of interest. No potential conflicts were declared.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Single-agent interleukin-2 in the treatment of metastatic melanoma: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Mar 20. Various p. (Practice guideline; no. 8-5). Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995; 13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 30, 2006. The updated information was verified by the guideline developer on July 7, 2006.

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